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THE INFLUENCE OF COMPLICATING DISEASES UPON LEUKÆMIA.*

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Investigations in leukæmia during the last decade have led to a great increase in our knowledge of the phenomena of that disease, especially of the minute changes in the blood and tissues. But the gains hitherto have added complexity to the subject by suggesting new problems, instead of clearing up the old ones. Failing the discovery of some microscopic germ as the cause from which the various changes can be traced, the elucidation of many details is likely to be brought about only by patient labor in piling up and analyzing observations.

With this idea I have examined one interesting feature, perhaps I should say one set of features in the disease, viz., the changes following or associated with intercurrent disease. Cases of this kind are rapidly multiplying in the literature, and, having had some instructive cases of my own, it seemed to me that a study of these and others might be useful. I soon found that the outcome would not be as rich as I hoped, but the subject seemed worthy of presentation on account of the nature of the material now available.

I will cite my most important case, leaving out many details of the history:

Case I. *Myelogenous (mixed-celled) leukæmia; influenza; reduction of leukocytes to* 5000 *and below; gradual rise of leukocytes six weeks after the complication, reaching* 157,000 *in another month;*

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* Read before the Academy of Medicine of Cleveland, September 18, 1903.

death seventeen months after the complication.—Mrs. C. D. A., aged forty-two years, housewife, was first seen December 29, 1896. From the notes made then I quote: Patient complains of swelling in the left side, shortness of breath, and weakness. The family history is negative as regards ancestors. The husband, who seemed well during the patient's lifetime, developed splenic anæmia a year after her death. (See *Transactions of Association of American Physicians*, 1903.) The daughter, after the mother's death, had lymphoid hyperplasia in the pharynx and tongue and in the appendix. The latter was the seat of frequent and severe pain; it could be felt as a hard body, as thick as a lead-pencil, through the strong and well-nourished abdominal wall, and was removed at my advice and found to be free from evidences of inflammation, but with lymphoid tissue unusually developed.

Besides the usual acute infectious diseases, the patient had ague twice in childhood, but does not think she had enlarged spleen, "ague-cake" being a familiar sign in that vicinity at the time.

Menstruation began at thirteen years, and was always regular, except during pregnancy, up to two years ago. Since then the flow has been greater, but pale, and accompanied by bearing-down pains.

At nineteen years she had "dysentery," passing blood with the stools for one month. A series of furuncles on the arms and back followed this. She was then fairly well for ten years, was married, and, except for an abortion after the first pregnancy, remained well until her second and last pregnancy, eight years ago. About the fifth month she had a pain in the abdomen, back, and right shoulder, which closely resembled biliary colic. The patient ascribes all her trouble, however, to the confinement, which was difficult, but the exact results of which do not appear. Three months after it she became intensely jaundiced, and remained so for two weeks. The abdominal pain mentioned above returned then, and at intervals, but without jaundice, up to two years ago.

Two years ago the patient thinks the present disease began, with chilly feelings in the back and hands. In two days there was pain in the splenic region, sore throat, pain in the extremities, and slight fever. The chills lasted for two months, occurring sometimes twice a day, followed by fever and sweating. The pain in the left side continued up to six weeks ago. It was thought to be pleuritic. Three months ago the swelling on the left side was discovered by the patient. It was then about the size of an apple. Soon after the swelling was discovered the chills and fever returned, with paroxysms, usually about 11 A.M. and 2 or 3 P.M., but any exertion was likely to be followed by a chill. The tumor gradually became larger. About two months ago a throbbing pain began in the posterior part of it, and lasted about a month. Then severe and unexplained vomiting came on, and in a paroxysm of vomiting it seemed as if something had fallen in the splenic region. Since then the pain has been less severe. Shortness of breath on exertion has increased gradually in the last year. There have been no hemorrhages. Headache has been troublesome for some months.

Status præsens, December 29, 1896. Patient is of small size, medium frame, muscles and panniculus well nourished. The superficial lymphatic glands are not enlarged. The face and visible mucous membranes are of good color, but the hands are pale.

The thorax is symmetrical in the upper part. Examination of the lungs negative.

The heart is in the normal position; dulness not enlarged. There is a soft systolic murmur all over the heart area; the first sound is loud. Radial pulse small, quick, regular.

The abdomen is large, especially in the left upper part, where the thorax is also fuller. The recti are separated. The lower edge of the liver is almost at the navel line, but deep in the abdomen. The edge is thin and tender on pressure.

The splenic dulness begins in the seventh interspace and extends down into the mass below the ribs, evidently the spleen, which can be easily felt as a flattened body reaching to the level of the anterior superior spine of the ilium and to the median line. The edge is thick; there is a shallow notch on the inner side. There is palpable and audible friction over the surface. The patient says the mass is sometimes lower than at present. It is not unusually movable by pressure or position.

There is pain on pressure over the sternum and tibiæ.

The blood is pale, not very thin; fresh preparations show enormous increase of the leukocytes, among which large cells with fine or coarse granules are conspicuous. The blood count shows: red corpuscles, 2,500,000; leukocytes, 367,070; hæmoglobin (Fleischl), 50. Stained preparations show moderate poikilocytosis, many nucleated reds—1:40 leukocytes, or 9074 per c.mm. About one-fourth have the size and appearance of megaloblasts, but the two forms run into each other by variations impossible to classify precisely. Differential count of the leukocytes shows: lymphocytes, 0.3; mononuclear neutrophiles, 48.8; polynuclear neutrophiles, 41.6; polynuclear eosinophiles, 0.7; mononuclear eosinophiles, 1.4; basophiles, 2; degenerated, 5. The lymphocytes are often smaller than red corpuscles, but do not show as intense staining of the nucleus as do typical small lymphocytes, and have usually a distinct rim of protoplasm. Many of the myelocytes have deeply indented nuclei, but the looser, skein-like structure of the nucleus distinguishes most of them from those denominated polynuclear. The eosinophiles, especially the mononuclears, vary much in size from that of a small lymphocyte to that of the largest mononuclears. The basophile cells are large or small in about equal proportions. The degenerated leukocytes are hard to classify, but seem to represent all the larger forms.

The diagnosis of myelogenous, mixed-celled leukæmia was given, the usual prognosis stated to the husband, and Fowler's solution recommended to the family physician.

February 1, 1897. The patient entered the medical clinic of the University Hospital. She says that two weeks ago she had influenza, with tonsillitis and coryza. The discharge was bloody, especially in the morning, and a week ago there was moderate nose-bleed. She complains now of great weakness, dyspnœa, pain in the left side, and general itching. She "feels as if walking on sticks."

Status præsens. The patient looks somewhat more anxious than before. The skin is not very pale. The hands feel numb when the arms are fully extended. There is no distinct tenderness over the nerve trunks of the extremities. The tongue is clean. There are no stomach symptoms. The pharynx shows moderate redness and swelling, with scanty mucopurulent exudate. The thoracic organs are negative, aside from a few small rales in both bases on deep inspiration, and a soft systolic murmur over the base of the heart. The abdomen is above the level of the ribs. The edge of the liver is within an inch of the navel line. The spleen extends three fingers' breadth below the margin of the ribs. The lower end is rounded, a shallow notch can be felt just above the point. The spleen is very tender on pressure, freely movable. There is distinct friction over it. The superficial lymphatic glands are not enlarged. There is no œdema of the ankles. The blood count: red corpuscles, 2,540,050; leukocytes, 7500; Fleischl, 50 per cent. Red corpuscles show marked vacuole formation; many polychromatophiles; some red corpuscles show mitotic figures. The arsenic had been increased up to 12 drops t. i. d.; it was continued, with extract of red bone-marrow (4 c.c. t. i. d.).

February 2d. Red corpuscles, 2,500,000; leukocytes, 8125; Fleischl, 50 per cent. Differential counts given in table.

7th. Patient complains of more numbness and also of itching. Arsenic stopped. Temperature has been up to 101° to 101.6° F.; pulse, 110; respiration, 22.

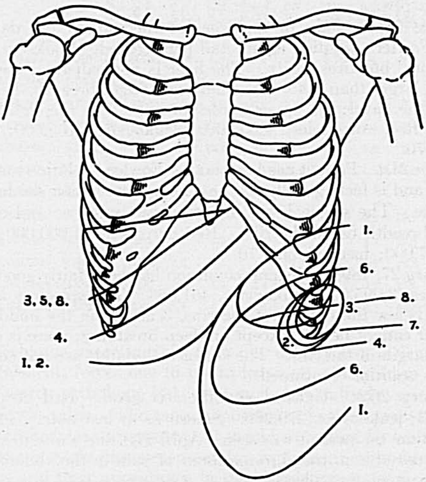
9th. Red corpuscles, 2,192,000; leukocytes, 4775; hæmoglobin, 50 per cent. Temperature has not been higher than 99.4° F.; pulse, 80 to 100; respiration, 22. Patient still complains of itching, also of weakness, headache, and slight dizziness.

12th. Red corpuscles, 2,863,000; leukocytes, 5000. The condition remained about the same. The temperature was rarely above normal; there was slight gain in weight. Itching was the most troublesome symptom.

March 3d. The leukocytes number 35,156; red corpuscles, 3,733,333; hæmoglobin, 60. The spleen can barely be felt on quiet breathing. On deep inspiration it extends three fingers' breadth below the ribs. Splenic dulness begins on the ninth rib and is 9 cm. long. On the right side there is dulness from the sixth intercostal space to an inch above the margin of the ribs and to the tip of the ensiform. The abdomen is slightly distended; no enlarged glands can be felt in it. The inguinal glands are slightly enlarged.

10th. Red corpuscles, 3,125,000; leukocytes, 40,170; hæmoglobin, 55. The systolic murmur over the base is still present. There is no œdema.

21st. Red corpuscles, 3,100,000; leukocytes, 90,000; hæmoglobin, 70. The patient feels better than before. Has no subjective symptoms. The spleen can barely be felt on quiet breathing; liver not enlarged. Patient has gained eight pounds in all since admission.



Variations in size of liver and spleen at different stages.

April 2d. Red corpuscles, 3,281,200; leukocytes, 157,000.

5th. Patient is going home. Feels very well. Spleen and liver as at last note. Red corpuscles, 3,580,000; leukocytes, 189,000. Continues Fowler's solution.

15th. Red corpuscles, 3,825,000; leukocytes, 217,600. No subjective symptoms; spleen as before; slight œdema of feet.

June 4th. Red corpuscles, 3,600,000; leukocytes, 307,000. Next day, at home, patient had a chill, followed by several others in the next twenty-four hours, and for the next three weeks had a good deal of fever. Severe pain in the splenic region required the use of morphine for sixteen days.

July 1st. Red corpuscles, 3,600,000; leukocytes, 307,000. The patient feels as well as before the febrile attack. She has tingling in the toes and fingers; otherwise well. She has gained eight pounds since leaving the hospital. The spleen is three fingers' breadth below the margin of the ribs on quiet breathing; it is hard and thicker than before. The liver is three fingers' breadth below the ribs, the edge thin and of normal consistency. Fowler's solution, stopped during the fever, renewed.

22d. Feels better. Took Fowler's solution up to 10 drops. The hands are better; the feet tingle slightly. Red corpuscles, 3,600,000; leukocytes, 178,000. The spleen is slightly smaller. Is now taking bone-marrow.

August 19th. Pain in the legs returned about ten days ago. Began Fowler's solution again, and pain ceased. Looks well; does housework, but tires easily. The liver is not palpable; the spleen is much larger than before, reaching two finger-breadths below the level of the navel; the upper border of dulness in the eighth interspace. Red corpuscles, 4,000,000; leukocytes, 165,000; hæmoglobin, 70.

October 21st. Patient has been taking Fowler's solution and bone-marrow and is feeling well, and now looks better than she has for a long time. The spleen is smaller, reaching only two and one-half fingers' breadth below the ribs. Red corpuscles, 4,000,000; leukocytes, 57,000; hæmoglobin, 70.

January 27, 1898. General condition has been fairly good. Red corpuscles, 3,095,000; leukocytes, 461,666. The spleen is a hand-breadth below the margin of the ribs, 3 cm. from the middle line. The liver cannot be felt, except on deep breathing; there is dulness to the margin of the ribs. The superficial glands are not enlarged. Fowler's solution continued.

February 26th. General condition is good. Red corpuscles, 3,533,333; leukocytes, 279,260. Spleen as at last note. This was the last time the patient was seen. April 17th she wrote to say that she was not able to travel, on account of pain in the abdomen and enlargement of the spleen.

June 8th. Reported that patient, who had been trying to come to the hospital, had fever, chills, nausea, and vomiting, and was very weak. "The spleen fills the entire abdomen."

17th. "Patient is able to sit up, but still very weak. Is entirely deaf and complains of roaring in the ears." Soon after this she died, while I was away from home. An autopsy was made, but no tissues preserved.

Summary of the case: A woman with mixed-celled leukæmia, with greatly enlarged spleen. Two weeks after an attack of what was probably influenza, the leukocytes were found reduced from 367,070 to 7500, falling to 4775 in two weeks more, with reduction, but not disappearance, of the abnormal white and red cells. The spleen was much smaller; the liver became smaller later. In two months from the complication the leukocytes reached 40,000, in ten weeks 157,000, and in a year 461,666, having once been as low as 57,000 in the mean time. The liver and spleen remained small for many months, though the spleen was usually easily palpable. For the next six months the patient grew worse in every respect, and died a year and a half after the first observation. The most important stages in the blood are shown in the following table:

Date.	Red cells.	White cells.	Hæmoglobin.	Nucleated red cells.	Small lymphocytes.	Large lymphocytes.	Transition and large mononuclear.	Polynuclear neutrophiles.	Polynuclear eosinophiles.	Mononuclear eosinophiles.	Myelocytes (Ehrlich).	Basophile.	Degenerated.
Dec. 29	2,500,000	367,070	50	9074	0.00	0.30	00.0	41.6	0.7	1.4	48.8	2.0	5.0
Feb. 1	2,541,050	7,500	50										
" 2	2,500,000	8,125	50	2358	4.2	5.7	4.9	70.6	......	......	12.3	......	6.0
" 9	2,192,000	4,775	50	1224	2.5	11.8	10.1	56.0	......	1.4	11.1	1.0	6.0
" 12	2,863,000	5,000	...	416	1.6	13.3	3.3	63.8	0.3	0.6	9.6	1.0	6.6
March 3	3,733,333	35,156	60	524	0.4	7.6	7.1	66.2	0.2	......	15.5	......	2.7
" 10	3,125,000	40,170	55	362	0.15	5.2	2.4	54.4	......	......	20.9	......	16.4
" 14	3,125,000	40,170	50	500	0.8	2.4	1.4	62.0	......	0.2	29.9	......	3.8
" 21	3,100,000	90,000	50	few	0.1	2.3	3.2	63.7	0.4	0.2	22.3	......	6.4
Oct. 21	4,000,000	57,000	70	1760	1.3	3.5	7.7	62.0	1.2	1.3	20.8	0.9	2.3
Jan. 27	3,095,000	461,666	65	7387	2.3	1.3	4.4	63.2	0.4	0.7	27.0	......	0.7
Feb. 26	3,533,333	279,000	70	6700	8.8	6.0	3.0	41.0	1.0	0.3	34.0	1.0	5.0

Such a change, more marked than one usually sees in leukæmia under treatment, forces one to try to learn something from it, not only as regards pathology, but, even more imperatively, something of therapeutic value. The most important objective symptom, the excess of leukocytes, disappears. It would seem that by examining such cases one might discover something regarding the production of leukocytes and their appearance in the circulation, as well as their ultimate destruction; also something of the life of the red corpuscles, and of other details of the pathology of leukæmia. It might seem that the process could be imitated, and a symptomatic, if not a causal, treatment be discovered. Medical literature contains a number of such cases, though not so many as one might expect, remembering the vulnerability of the leukæmic to infection. Not only single cases have been reported, but studies have been made, and in the present article I am merely going over ground that has already been traversed by others, my only advantage being due to the fact that I am at present the latest inquirer.

The literature of the complications is unusually confused. Some of the cases have been reported two or even three times by the same or different authors. Besides unavoidable errors, such as those in ages, dates, and other minor details, author's names have been changed. H. Strangways Hounsell, one of the earliest authors, becomes Honsell, Hantell, Strongways, Srangways, and even, by an unnecessary comma, two authors, contributing a case each. Thorsch reported a case in his own name, from the clinic of von Limbeck, and at least two writers ascribe it to "Zeissl," whose name does not appear in the original article.

The subject is complicated by other things. A frequent cause is the lack of exact classification of the leukæmia. In many cases I have been obliged to follow the author's terminology and classify cases that should, perhaps, be otherwise arranged. With future cases this difficulty will become less frequent, and also another regarding the diagnosis of the complication. But owing to the chronic and obscure course of many cases and the tendency of patients to wander from one to another physician, incomplete observations will multiply, and will, nevertheless, often deserve publication.

I shall discuss the cases according to the nature of the complicating disease in the first place, and the variety of leukæmia in the second, and, without trying to follow a scientific order, will speak first of tuberculosis.[*]

Cases of Tuberculosis and Leukæmia.

The combination of tuberculosis and leukæmia was noted very early. Virchow[1] described a case in 1849, and his rival, Bennett,[2] noted 2 out of 23 cases collected in 1852. Virchow also made the anatomical examination in a case observed clinically by Bamberger[3] in 1857. According to Mosler,[4] there were 12 examples of tuberculosis in the 100 cases of leukæmia analyzed in Martin Ehrlich's thesis in 1872. Yet in the recent literature the combination is rarely mentioned. Many authors admit that they have never seen such a case. It was encountered only twice in the 37 cases observed in the Göttingen clinic,[17] with 10 autopsies. Among my own cases, 25 in number, there were no clinical evidences, but in 2 out of 6 autopsies miliary tuberculosis was found, once in a marked degree. I think that more extensive observations will show that the exclusion is not so absolute as has been thought. In my own clinical material leukæmia occurs most frequently in the early part of the fifth decade, when tuberculosis is relatively infrequent. Cornet, Moorehouse, and others have pointed out that this age period is one very prone to tuberculous manifestations, but I think the whole subject is one that requires further investigation. This is one of many aspects of leukæmia that can be studied with advantage by the physician in private practice, where the whole course of the disease can be followed. Owing to the nature of the disease patients with leukæmia do not remain in hospitals as long as is desirable for extensive study.

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[*] Three articles were received too late to use in this paper. Tommaso Prodi, La Riforma Medica, July 22, 1903, A Case of Lymphatic Leukæmia, with Tuberculosis of the Larynx, Lungs, and Lymphatic Glands. W. J. Susmann, The Practitioner, October, 1903, Tuberculosis in One out of Forty-one Cases of Leukæmia Observed in Various London Hospitals. Wilhelm Neutra, Zeitschrift f. Heilkunde, Band xxiv., 1903, Two Cases of Lymphocythæmia; in one Pleurisy, with Leukocytes Dropping from 160,000 to 8800; in the other, Suppurative Pleurisy and Peritonitis; Blood Not Thoroughly Examined.

Another fact requires some consideration. Small leukæmic growths closely resemble tubercles. The early literature has occasional mention of leukæmic growths, sometimes of large masses that, especially in the lungs, break down and simulate ulcerative tuberculosis. At an early period Virchow, Boettcher, and Ollivier and Ranvier studied the peculiarities of the two growths, but it was not until the structure of tubercle had been more minutely described by Wagner, Schüppel, and Langhans, and especially after the discovery of the tubercle bacillus, that the differentiation was made certain. It would be interesting to re-examine some of the old museum preparations with reference to the breaking down of such growths. The analysis of cases published before 1882 is very unsatisfactory. The only cases necessary or profitable to examine now are those in which an effect on the blood or organs has been noted.

There are in the literature about 27 cases that either are cited in this connection or might be referred to. To these I add two imperfect observations not previously reported. The cases of Virchow and Bamberger, mentioned above, throw no light on the question now under consideration. That of Hounsell,[5] fairly well described, is of value also only in showing the association of diseases. Besides tuberculosis the patient had scarlet fever, tonsillitis, and secondary pneumonia. The leukæmia was probably acute lymphocythæmia. Ollivier and Ranvier[6] reported the case of a man, aged forty years, with miliary tuberculosis of the abdominal organs, old pulmonary tuberculosis, and leukæmia. The case cannot be analyzed for lack of details regarding the blood. The same difficulty exists in the report by Robin[7] of a case of extensive lymphatic tuberculosis with leukæmia. Still less available is a case mentioned by de Roth,[8] of miliary tuberculosis and leukæmia, observed by Knoepfelmacher, but not published. Brueckmann[9] has reported a case of splenic-myelogenous and lymphatic leukæmia with old and recent tubercles that has some incidental interest, because it appears that the examination of the blood made in a famous German clinic, in 1892, consisted in estimating the proportion of red and white cells in blood, "mit Wasser stark verdünnt." Two cases reported by Volpe[10] are even more imperfectly described, and do not add anything to the material, while several of 6 cases he quotes from the literature are cases of pseudoleukæmia. In a case of Musser and Sailer[11] there were "evidences of old tubercle" in the apex of one lung. This and a similar case reported briefly by Saundby[12] show that leukæmia can develop in bodies with old tuberculous foci, as is proved by some of the cases cited below. Sabrazès[13] has briefly mentioned a case of myelogenous leukæmia and tuberculosis of the lymph glands, with diminution of eosinophiles and mast-cells, and increased polynuclears. The patient reported by Strattmann[63] had a history of apical catarrh and pulmonary hemorrhages before the spleen became large, and may also have been tuberculous. The patient treated with tuberculin by H. Heuck,[64] mentioned below, also had slight signs of pulmonary tuberculosis.

Finally, in Kraus'[32] case, discussed below, there was miliary tuberculosis besides the streptococcus and diplococcus infections.

Of the other 15 cases 7 are examples of medullary leukæmia, with acute miliary tuberculosis. Of these, the cases of Quincke [14] [15] (2 cases), Lichtheim,[16] Schmidt,[17] Bezançon and Weil,[18] and Hirschfeld and Tobias[19] showed diminution of leukocytes as follows:

Quincke, Case 1	1 : 3	to	1 : 50
Quincke, Case 2	1 : 4	to	1 : 90
Lichtheim*	1 : 8	to	1 : 370 (250,000 to 8,900)
Schmidt	1 : 2.9	to	1 : 135 (962,000 to 28,000)
Bezançon and Weil	135,000	to	19,871, rising to 45,000
Hirschfeld and Tobias	331,000	to	110,937

In Schmidt's case there were small cavities in the lungs. In Hirschfeld and Tobias' case there were old lesions in the apices, but not cavities, and no clinical symptoms of tuberculosis. The miliary tuberculosis does not seem to have been very severe. No bacilli were found in sections. The leukocytes were as high as 434,000 nine months before the low count, 228,000 four months before, rising to 331,000 two weeks before the low count. Six months later, after a recurring pneumonia, they numbered 283,333, and death occurred five weeks later. In the case of de Roth[8] there was a rise toward the end.

Four cases of myelogenous leukæmia are recorded in which chronic tuberculosis existed, sometimes ending in miliary tuberculosis. These are reported by Elsner and Groat,[20] Sturmdorf,[21] Parker,[22] and Murrell,[23] though the tuberculosis in the latter case may not have been very chronic. In all there was a fall in the number of leukocytes toward the end. In some the lowest count was still so high as to leave little room for doubt as to the diagnosis, viz., in Elsner and Groat's case, 121,000; Sturmdorf's 116,000; Parker's, 100,000, later 130,000; but in Murrell's it was 16,200, from 220,000. Arsenic was freely used in this case.

The other cases show variations in the leukæmic condition and other features that make it necessary to consider them separately.

In the case of Stintzing[24] there was enlargement of the spleen and lymphatic glands, with old tuberculous lesions (cavities) in the lungs. The leukocytes decreased slightly, 1:100 to 1:150; the glands became smaller, but the spleen remained about the same size. It is difficult to understand the author's statement that the "leukæmia improved while the phthisis made great progress," particularly as the patient died, unless we take a very partial view of the case.

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* Elsner and Groat and Hirschfeld and Tobias classify Lichtheim's case among lymphatic leukæmias, but as the author says the polynuclear and mononuclear cells were about equal, I agree with Baldwin and Wilder and Quincke in placing it with the splenomedullary cases, though the lymph glands were also enlarged.

Juenger's[25] patient had enlarged lymphatic glands, and probably acute leukæmia, though the description of the blood leaves some doubt as to its precise character. Miliary tuberculosis of the glands and peritoneum, with early caseation, was found post-mortem. The leukocytes rose from 40,000 to 125,000 in two weeks, two and a half months before death, and fell to 68,800 six weeks before the end, following an attack of diarrhœa. Arsenical pigmentation was then present. The glands became smaller. An abscess in one of them was incised. The blood was not examined again until two days before death, and then showed no excess of leukocytes.

In Francksen's[26] case, probably also lymphatic leukæmia, there was tuberculosis of the lymph glands, spleen, and liver, with final bronchopneumonia. The leukocytes fell from 240,000 to 128,000 between observations four months apart, and did not fall lower in the next three days, or two days before death. The spleen became smaller toward the end.

Baldwin and Wilder[27] reported a case of probable chronic lymphocythæmia. In this lymphatic enlargement had lasted more than two years, chronic pulmonary tuberculosis, finally developing cavities, as long or perhaps longer. The leukæmia was observed for about two months. There were no recent miliary tubercles. The leukocytes numbered 695,000 at the beginning of the period, reached 1,113,000 nine days before the last count, and then fell to 943,500 and 959,500, without qualitative changes. The lymph glands and spleen grew smaller four days before the end.

From the available material it appears that chronic tuberculosis does not distinctly influence the course of leukæmia, or, as we shall see later, materially influence the leukocyte formula. Acute miliary tuberculosis, on the other hand, is followed by or associated with reduction of the leukocytes in the majority of cases. The exceptional cases may be due to the slight development of the miliary tuberculosis in extent, or to the fact that death occurs before the change has time to take place, though it may be, as de Roth has suggested, that in some cases the body becomes accustomed to the infection and the leukocytes are not affected, as in more acute cases.

Two of my cases, though imperfectly observed, add weight to both of the first two suppositions.

Case II.—M. T., domestic, aged twenty-five years, first seen June 2, 1896. "She was well until July, 1895, when swellings and red spots appeared on the right leg, and similar lesions appeared on various parts of the body up to the time of examination. The abdomen has been large for nearly a year. It was supposed to be due to uterine or ovarian tumor, for which an operation was advised by two physicians she consulted. Weakness present for three months." I found a mixed-celled leukæmia, with red corpuscles, 3,587,500; leukocytes, 598,000; hæmoglobin, 60. There were ecchymoses, up to the size of the palms, on the arms and legs. The spleen extended one inch beyond the middle line, and to the level of the anterior superior spine of the ilium. The liver was not enlarged; the axillary and cervical lymph glands were slightly enlarged, but not the inguinal glands. No pain or tenderness in the bones.

The patient was observed by Dr. Cowie and myself for two years, taking Fowler's solution as steadily as is usually possible. Within three weeks the ecchymosis ceased, menstruation reappeared after an absence of several months, but there was no marked fall in the leukocytes and no noteworthy change in the leukocyte formula. Myelocytes varied from 25 per cent. to 44 per cent.; polynuclears, 30 per cent. to 50 per cent.; lymphocytes, 1 per cent. to 6 per cent.; polynuclear eosinophiles, 1 per cent. to 3.2 per cent.; mononuclear eosinophiles, 1.2 per cent. to 1.8 per cent.

Becoming anxious for more radical treatment, the patient disappeared from our observation. A year later, three years after the first observation, Dr. Cowie and Dr. Warthin were given an opportunity of making an autopsy by the courtesy of Dr. J. A. Wessinger, who had been called upon in the last illness. The spleen was enlarged; the chief picture was that of a severe tuberculosis of the serous membranes. The blood showed no increase of leukocytes, and microscopic examination of the tissues revealed a complete absence of leukæmic changes, except in the bone-marrow, which was lymphoid.

In this case it is impossible to know when the change occurred. The tuberculosis was more severe than it seems to have been in many of the reported cases.

In Case III., to be reported more fully on account of other features, a man, aged twenty-nine years, died with so-called leukæmic apoplexy, without any decrease of leukocytes up to the moment of death. At the autopsy a slight recent miliary tuberculosis was found. Striking as the differences are in these two cases, I think we should await the publication of others before drawing conclusions from them.

Miscellaneous Infections.

There are 23 reported cases of intercurrent infection other than tuberculosis, including my own Case I. The infections represented are: In medullary or splenomedullary leukæmia: typhoid-like disease (Eisenlohr[28]), afebrile typhoid (Pal[29]), erysipelas (Richter[30]), also reported by Freudenstein;[31] erysipelas, streptococcus, and diplococcus infection with miliary tuberculosis (Kraus[32]), sepsis (H. F.

Mueller,[33] Koermoeczi[34]), empyema (G. Heuck[35]), influenza (Kovacs,[36] Dock), peritonitis (Da Costa[37]).

In lymphatic leukæmia, acute in most cases: sepsis, angina (H. F. Mueller[38]), angina, streptococcus (Weil[39]), streptococcus infection (Wende[40]), sepsis (Cabot[41]), staphylococcus (Fraenkel[42]), colon bacillus (Fraenkel, *ibid.*), staphylococcus and colon (E. Mueller[43]), pneumonia (Oette,[44] Froelich,[45] Thorsch[46]).

Chronic lymphocythæmia was observed complicated by pneumonia by Grawitz[47] and Hart,[48] and bronchitis by Petit and Weil.[49] In some of the cases more than one complication was observed, and these I shall utilize as far as the data will permit.

The following may also be mentioned: Heusner, in discussing Strattmann's case,[68] mentioned a patient with leukæmia in which diminution in the size of the glands and spleen and improvement of the blood followed pneumonia, but relapsed. Rieder[50] (p. 38) has reported a case of medullary leukæmia with sepsis, and one of lymphatic leukæmia and sepsis, with increase of the leukocytes. The details are too scanty to use. The case reported from Mosler's clinic by Oette[44] may be mentioned here, though I might have included it among the more important cases. A girl aged twenty-three had fever with icterus. The leukæmic blood improved after six weeks, and six months later was "almost normal." The case is of great historical interest, and Oette's thesis of much value, but the case cannot now be compared with others. Chantemesse, in the discussion of Bezançon and Weil's case,[18] mentioned a patient of his who acquired erysipelas in the course of leukæmia.

Of the cases referred to above, there was a marked decrease of leukocytes to or near normal in 11, viz., those of Eisenlohr, Kraus, Wende, Froelich, Fraenkel (2 cases), Oette, Koermoeczi, Dock, E. Mueller, Cabot. There was a relatively slight fall in 9, viz., those of Pal, Richter, H. F. Mueller, Weil, Thorsch, G. Heuck, Kovacs, Hart, Grawitz. No change or a rise in 3, viz., Mueller, Petit and Weil, Da Costa.

The cases differ so much in detail that it is difficult to make comparisons. Taking first streptococcus infections, we find that in Richter's case of facial erysipelas following puncture of the tympanic membrane, the leukocytes had fallen on the second day of the complication to 56,000 from the 320,000 of two weeks earlier. The spleen was smaller, and in three days more was 4 cm. less in length, 3 cm. in width. The leukocytes sank to 29,000 on the fourth day, but rose rapidly to 148,000 on the sixth day, along with the development of an abscess of the eyelid and bronchitis, and fell to 52,000 in six more days, while the general and local conditions improved.

In Weil's case of angina with streptococci in the blood, the leukocytes fell during blood infection from 290,400 to 75,682 in four days; seven days later, 66,230. The author thought the angina had increased the leukocytes (the blood had not been examined before), which he estimated at 60,000 to 80,000. I can see no ground for this assumption.

In Kraus' case there was in the beginning a leukocyte count of from 360,000 to 420,000. The complication, a streptococcus and diplococcus infection of the bronchi with miliary tuberculosis, ran a somewhat obscure course, the blood symptoms being the only marked ones. After slight physical signs of bronchitis, blood-streaked sputum appeared, with fever and increased size of the spleen. The leukocytes were then 393,400, but fell to 251,600 in about seven weeks, during which there was erysipelas. Two weeks later the count was 240,000. In three weeks they numbered 390,000, in four weeks 504,000. The bloody sputum then contained the cocci mentioned. The sputum then ceased; there were no signs of pneumonia. In three days the leukocytes fell to 120,000, in eight days more to 4600, without myelocytes, mononuclear eosinophiles, mast-cells, and nucleated reds, but with many degenerated leukocytes. The spleen became smaller in the next few days. The leukocytes rose to 9000; death followed four days after the last count. Autopsy revealed pneumococci in the purulent exudate in the peritoneum and in the spleen and liver, bilateral pneumonia, purulent pleural exudates, pylephlebitis, and tuberculosis of bronchial glands, lung, larynx, peritoneum, and liver. The anatomical diagnosis of leukæmia could not be made. What part the various infections played is difficult to say, but the streptococci do not seem to have been so much concerned as the diplococci. The tuberculosis was probably too slight to be effective.

In one of Pal's cases of medullary leukæmia with bronchitis and erysipelas the leukocytes rose from 75,000 to 105,000 in two days Tracheotomy was necessary, and death occurred a week later.

In Wende's case, lymphatic leukæmia with streptococcus infection, there was a marked fall, 45,000 to 600.

In Thorsch's case of pneumonia in lymphatic leukæmia (also cited by von Limbeck[51] and sometimes referred to as Zeissl's case) there was a rapid fall in the beginning from 119,000 to 43,500 by the fifth day. Next day there was an extension of the disease, and in three days more the leukocytes rose to 172,000 on the morning of the day of death, 133,000 in the afternoon.

Froelich's case was probably one of lymphatic leukæmia, though the author called it pseudoleukæmia. Under complicating pleuropneumonia the leukocytes fell from 66,667 (having been 309,000) to 8823 in the last week.

In Oette's case of chronic pneumonia the data are insufficient for analysis. He mentions two cases from the older literature showing that bronchopneumonia does not always alter the blood picture in leukæmia, as it had in his own case.

In chronic lymphocythæmia 2 cases have been reported complicated by pneumonia. In that of Grawitz the leukocytes, "already rather low," sank lower in the beginning and rose to a considerable height in defervescence. There was no change in the formula.

In Hart's case there was a fall of from 1,168,000 to 450,000 on the fourth day of pneumonia. Death occurred two days later.

The 2 cases of influenza cannot be compared with accuracy, because in 1, my own, the diagnosis was based on the anamnesis only. In Kovacs' case the leukocytes, only 67,000 at the highest count, though they had been higher, apparently, fell to 17,000 eleven days later. Six days later there were 33,000. The patient also had bronchitis, pneumonia, and otitis. In one of H. F. Mueller's cases the patient gave a history of influenza, not observed by the author, with diminution in the size of the enlarged glands, which regained the original size after the fever subsided.

The various cases reported as examples of sepsis complicating leukæmia cannot be compared with advantage, but some of them have points of interest that deserve mention. One of the first was the case of H. F. Mueller.[38] A man with lymphatic leukæmia, with 180,000 leukocytes, had a subperiosteal abscess in the right leg. A count made then, three weeks after the former one, showed 400,000 leukocytes. The glands were about a third their former size; the spleen was also smaller. Death ensued four days after the last count. In Cabot's case of sepsis in lymphatic leukæmia there was a sudden fall from 40,000 to 5661 in one week, and a progressive fall to 471 in nine days more. In Koermoeczi's case of myelogenous leukæmia with sepsis, originating in the nose and leading to hemorrhagic pericarditis without bacteriæmia, the leukocytes fell from 100,000 to 2000. In H. F. Mueller's case of myelogenous leukæmia there was sepsis following abscess from therapeutic injections. The leukocytes had already fallen from 406,200 to 246,900, influenza having been passed through. They then fell to 225,000 with the onset of sepsis, and in the following seven weeks reached 75,500. Pleurisy and pneumonia then developed, and ante-mortem, eighteen days after the last count given, there were 57,300 leukocytes. The spleen was smaller in the later stages; the leukæmic character of the blood was lost.

In both of Fraenkel's cases of acute lymphæmia, one of staphylococcus infection, the other colon infection, there was a marked fall from 123,000 to 600 in twelve days, and 220,000 to 1200 in sevendays.

In E. Mueller's case of acute lymphæmia with streptococci, staphylococci, and colon bacilli in the exudate in the pharynx, the leukocytes fell from 109,600 to 6800 in five days, 39,200 in the last twenty-four hours.

In Eisenlohr's case of typhoid-like infection, the leukocytes, enormously increased before, fell to almost normal. An attack of follicular angina was followed by an increase, which did not subside in the remaining four weeks of life.

In Pal's case of afebrile typhoid there was a fall from 991,000 to 650,000 in sixteen days, most of it in eight days. Death occurred a week later. Pal could not see that the typhoid infection (not suspected during life) had any influence on the blood or other clinical phenomena. Besides the typhoid there was jaundice, and a traumatic, suppurating hæmatoma.

In G. Heuck's case of empyema there was a variation of from 400,500 to 80,100, rising after thoracotomy to 169,800.

I have already mentioned H. F. Mueller's case, in which the leukocytes increased during infection. Two other similar cases have been recorded. In the case of Petit and Weil there was chronic lymphocythæmia. Bronchitis occurred, fatal on the sixth day, after diminution of the enlarged glands. The leukocytes increased in the period from two days before bronchitis to the last day from 202,238 to 398,866. Da Costa[37] mentions a case of splenomedullary leukæmia, in which, within ten days after the onset of peritonitis, the leukocytes rose from 245,000 to 400,000.

The cases just cited are of importance chiefly in a suggestion they offer. In all three the rise of leukocytes was discovered early in the complication; the patients died soon after. It is possible, of course, that a fall might have occurred after the rise had the cases ended less abruptly. The earliest period after complication has rarely been carefully observed and should be thoroughly studied in future.

From the foregoing it appears that in the great majority of cases intercurrent infections cause a decrease of the leukocytes in leukæmias of various kinds. The fall may be so slight as to leave the gross picture of leukæmia unchanged, but in about half the cases the white corpuscles fall to normal or below. It is interesting to note the extreme leukopenia that occurred in some cases: 600 in one of Fraenkel's, 1200 in another, 600 in Wende's, 471 in Cabot's, 2000 in Koermoeczi's.

Besides the leukocyte decrease, the organs, enlarged as the result of the leukæmia, became smaller. In some cases the organs became smaller later than the fall of leukocytes (Quincke[14]), sometimes earlier, in others simultaneously; sometimes the organs became smaller without diminution of leukocytes (H. F. Mueller, Petit and Weil). The diminution was sometimes very rapid. Quincke estimated the change in the volume of the spleen in one case at 100 grams a day, a loss that I think must have been exceeded in my own case. It is often difficult to distinguish between this change in the organs and that observed in some cases of leukæmia a short time before death. Sabrazès mentions a case in which cutaneous neoplasms became smaller during a terminal infection, but from the original report* I cannot see anything peculiar, especially as the patient was taking arsenic and quinine at the same time.

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* Liffran, J. Contribution a l'étude de la leucocythémie aigue, Thèse, Bordeaux, 1898, p. 66.

Changes in the Red Blood Corpuscles.

Changes in the red cells have not been studied as carefully, perhaps, as they deserve in complicated leukæmias. Out of 18 cases in which the reports are full there was a rise in the number of red cells, simultaneous with the fall of leukocytes, in 8. The difference was often slight, but in 6 it was 500,000 or more (once 1,300,000) per cmm. (Lichtheim). In the other cases the rise was insignificant, or there was a fall. The latter was 500,000 or more in 4 cases; in 1 1,200,000 (Juenger). The great variations in the red count in leukæmia without complications should be borne in mind. A difference of a million or more may be observed in a short time independent of visible causes. The frequency of the rise in the red cells, while the leukocytes and other symptoms seem to indicate the opposite process, suggests a change in the blood fluid as the cause. The fact that 4 cases with marked rise occurred in tuberculosis (Lichtheim, Schmidt, Sturmdorf, de Roth) is interesting, but the cases do not offer a satisfactory explanation. Quincke noticed the unusual bloodlessness for leukæmia, post-mortem, in 1 of his cases. In my second case of tuberculosis the vessels were unusually full of blood.

The histological changes in the red corpuscles are interesting, but variable. Nucleated red cells are not always absent, as some have thought. In Richter's case they appeared during the complication. De Roth noticed many, including some in mitosis. In Juenger's case they were pretty numerous, but disappeared two days before death. In my case these cells were less numerous than before the complication, and increased as the leukocyte count regained a high point, but there were many, even at the lowest period, and often in mitosis. The condition of the red corpuscles should be carefully observed in future.

Qualitative Changes in the Blood, Especially in the Leukocytes.

The earlier observers were unable to notice the finer details in the cells, on account of the lack of methods. Mueller mentioned, in reporting his first case, that mitotic cells (myelocytes) disappeared almost entirely, and the leukocytes changed, so that the leukæmia seemed better, judging from the blood. Mueller's second case, with increase of the leukocytes, has often been misquoted. He himself admitted that no accurate examination of the blood cells had been made. He thought there might have been an increase of polynuclears, as occurs in sepsis, but he also thought the new cells might have been derived from the shrinkage of the enlarged glands, in which case they would hardly have been polynuclear.

Kovacs noticed in his case of influenza with slight decrease of leukocytes that the myelocytes disappeared almost completely, the eosinophiles also, the mitotic cells and nucleated reds completely.

There was an increase of polynuclear cells, so that the blood picture was that of leukocytosis. With the rise of leukocytes the marrow elements reappeared.

Fraenkel noticed no increase of polynuclear cells in his first case, in which, however, the examination was not thorough. In his second case all varieties were reduced.

Richter observed disappearance of mononuclear cells during the complication, with increase of polynuclears up to 90 per cent., the latter in the secondary rise with abscess. Before the complication the two classes had been about equal.

Thorsch, whose case appears to have been chronic lymphocythæmia, with mononuclear cells about 97 per cent., and no eosinophiles or nucleated reds, says that the changes were: mononuclears, 138,600; polynuclears, 1400 at one extreme and 40,585 to 4915 at the other, showing an absolute increase of polynuclears. But this was by no means such an increase as would cause distinct leukocytosis in a non-leukæmic subject, and before the complication, with 113,000 leukocytes at one time, there were 4520 polynuclears. Thorsch suggested that relative increase of polynuclear cells is observed by all in complicated leukæmia, and he made H. F. Mueller's case one of the number, but, as I have shown above, without sufficient basis. Hirschlaff* has a reported case showing that the polynuclears can increase markedly in leukæmia without infection.

In Lichtheim's case of tuberculosis with a fall of 250,000 to 8900, there was a relative increase of polynuclears, viz., from 50 per cent. to 90 per cent., which would amount to a slight increase above normal, but far below the polynuclear count at the height of the leukæmia.

In Baldwin and Wilder's case, without marked alteration of the blood count, there was no notable change in the leukocyte formula.

In Koermoeczi's case of sepsis, with a fall of from 100,000 to 7300, the eosinophiles, myelocytes, and mast-cells disappeared. The polynuclear neutrophiles numbered 75 per cent. (possibly 70 per cent.; there is an error in the report). Just before death counts of 3000 and 2000 were made, with slight increase of the lymphocytes, but no other change.

Adler[32a] examined the blood from Kraus' case, with special reference to the leukocyte formula. Kraus had reported disappearance of the myelæmic condition and the appearance of degenerated leukocytes. Adler shows in tabular form the fall and ultimate almost complete disappearance of the mononuclear neutrophiles (25.50 per cent., 100,514 cells to 0.40 per cent. and 18 cells), the complete disappearance of the basophiles and mononuclear and polynuclear eosinophiles. In the rise before the final fall there was an increase of lymphocytes and decrease of eosinophiles. The eosinophiles disappeared completely with the beginning of severe septic phenomena, and the lymphocytes (small) increased to 40.80 per cent.; large lymphocytes, 1.80 per cent.; mononuclear neutrophiles, 0.40 per cent.; polynuclear, 58.80 per cent., the latter being only slightly increased relatively.

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* Deutsche med. Wochenschrift, 1898, Vereins-Beilage, p. 162.

Bezançon and Weil noticed in their case of tuberculosis that the leukocytosis was polynuclear during the infection, instead of mononuclear; basophiles, mononuclears, and eosinophiles were few. There were no nucleated red cells, whereas before there were many, some of them in mitosis. Later, as the infection advanced, the leukocytes rose again (from 19,871 to 45,500), and myelogenous cells, with nucleated reds, increased. In the case of Petit and Weil there was no notable change in the formula. In the case of Weil the polynuclear cells were relatively as well as absolutely diminished; the eosinophiles also.

In Elsner and Groat's case there was an increase of polynuclears and lymphocytes, relatively, and a diminution of myelocytes, as the tuberculosis advanced. But not only in the number of leukocytes, at the lowest 121,000 cells, but also in the formula, the leukæmic character was preserved: polynuclears, 68; myelocytes, 17.5; lymphocytes, 6.5; eosinophiles, 5.2; many normoblasts and megaloblasts.

Sturmdorf observed in his case, in which the number of leukocytes was not much altered during the observations, that each rise in temperature was accompanied by an increase of polynuclears and decrease of myelocytes, "suggesting an intercurrent leukocytosis."

In Wende's case, with a drop of from 45,000 to 600 leukocytes, there was an increase of polynuclears of from 3.4 per cent. to 10 per cent., and a decrease of lymphocytes from 95 per cent. to 88 per cent. in nine days. There are some discrepancies in the author's figures, but they do not materially affect the statements.

In the case of Hirschfeld and Tobias, with a fall only to 110,937 (from 424,000), the polynuclear cells were not relatively increased; the myelocytes were lower then than when the count was above 400,000, but higher (11.5 per cent.) than when it was 300,000 (7.6 per cent.), and there were other variations, but as the author shows, by the counts of another leukæmic patient, the variations were no greater in the case of infection than are sometimes observed without it.

In Murrell's case there was a marked fall in the number of myelocytes, though the differential counts are unusual and cannot be readily compared with others. For example, the eosinophiles are given as 20 per cent. with counts of 20,000 and 29,000; none with 16,200; besides which it is said the myelocytes, 20 per cent., 44 per cent., and 7 per cent. on different days, were chiefly eosinophile.

Parker states that in the low count, 130,000, the polynuclears were relatively fewer than at the height of the leukocytosis, 70.8 per cent. and 57 per cent.; the myelocytes high, 25 as compared with 14; the other forms not notably altered.

Hart found no noteworthy changes in the blood in his case of lymphocythæmia.

Grawitz noticed no change in the formula, either in the fall in the beginning or the rise after the pneumonia or after a turpentine abscess with temporary low count.

In my own case the polynuclears were relatively and absolutely about the same as in normal blood. The lymphocytes were relatively and absolutely about normal, relatively higher than in the high stage, but absolutely slightly lower. The polynuclear eosinophiles were relatively and absolutely low, the mononuclear eosinophiles relatively lower than before, but still considerable, and even higher relatively than at later periods with excessive leukocytosis. The (Ehrlich's) myelocytes were relatively and absolutely low, but even at the lowest count, 9.6 per cent., higher than is usually found in any accidental myelocythæmia. Mast-cells were relatively as in other stages. Degenerated leukocytes were relatively about as high as in the first observation, but higher than they became later as the count rose. Nucleated red cells were relatively much higher than before, reaching 1 to 2.4 at one time, or absolutely 2090 per c.mm. One-fourth were megaloblasts, and a few of these were in mitosis. Nucleated reds were absolutely more numerous at the first count, 1 to 40, or 9074 per c.mm., with a few in mitosis. A few myelocytes also were in mitosis. The reds showed poikilocytosis, vacuoles, and variations in size, as well as polychromatophilia, but without notable changes from the earlier count. No Charcot crystals formed in blood kept for several weeks, and not until the leukocytes had risen to 35,000.

During the rise of leukocytes that began between two and four weeks after the fall was discovered the formula was altered by the relative decrease of lymphocytes, the relative increase of myelocytes, and a slight relative increase of eosinophiles of both kinds. The nucleated reds increased slowly. The large number of these cells during the low leukocyte stage is exceptional. It is possible that they were fewer or absent in the preceding two weeks immediately after the infection, and that they began to reappear in the stage of reaction, but the counts do not support this view.

It appears, then, that the changes in the leukocyte formula are not uniform, though there is a disposition for the leukæmic character to disappear more or less completely under the influence of infections and for the polynuclears to increase absolutely as well as relatively.

When Does the Change Occur?

When the change occurs is a question that cannot be answered very fully, on account of the small number of cases in which the process could be observed from the beginning.

In Eisenlohr's case the glands and spleen diminished daily from the beginning of the infection and the blood changed simultaneously. As the glands and spleen enlarged again, the blood resumed its former leukæmic character. The decrease lasted fourteen days. One month after the decrease the blood showed proportions of 1 to 4.

In Kovacs' case the blood resembled that of leukocytosis nine days after the beginning of the infection. In twelve days the spleen was smaller and softer. On the tenth day there were few myelocytes; no nucleated reds. Three days later there was an increase, with many myelocytes, and in three more there were 33,000 leukocytes.

In Fraenkel's first case the whole process took place in twelve days. In his second one the leukocytes had fallen to 47,000 by the seventh day, 3800 by the eighth day, 1200 by the tenth day.

In Richter's case the leukocytes fell from 56,000 to 29,000 in two days, but two days later they were 148,000, and six more 52,000.

In Thorsch's case the lowest point was reached in four days. Death occurred three days later.

In Lichtheim's case there was a slow and steady decrease for two months, when death occurred.

In Koermoeczi's case, eight days after a count of 100,000, the leukocytes had fallen to 7300. The patient lived five days longer, with almost the same blood picture.

In Kraus' case the leukocytes fell quickly after infection, viz., from 120,000 to 4600 in one week. In five days more the leukocytes had increased to 9000, and in four more the patient died.

In Weil's case the fall from 270,000 to 75,682 took place in six days; in seven more the number was 66,230.

Elsner and Groat noted a gradual fall of 200,000 leukocytes in three months.

In Wende's case, sepsis in acute lymphocythæmia, the leukocytes fell in nine days from 45,000 to 1600. In Cabot's case the fall to subnormal took only sixteen days; in E. Mueller's case five days.

In Murrell's case there was a fall in three days of from 150,000 to 20,000. Then an increase six months later, and another fall from 167,000 to 16,200 within five weeks.

In my own case of influenza the fall of from 367,070 to 7500 probably occurred within two weeks, but there was no actual observation in that time.

In general, the fall occurs soon after the infection, more promptly in acute than in chronic infections. The cases of chronic infections, however, are too few and too diverse in character to enable us to draw sweeping conclusions. There are also too few cases observed from the beginning to ascertain the first effects of the infection (or intoxication). Perhaps these differ in various cases.

As regards changes in the formula, Hirschfeld and Tobias give a table showing that variations can be observed in the leukocyte formula quite apart from complications, especially notable in the polynuclear and myelocyte count. This will be confirmed by all who have followed up cases of leukæmia for some time, while changes in the gross number of cells, both red and white, are equally common, and often quite as much or even more marked than in some of the cases examined above.

A very interesting fact brought out in some of the cases, and one that I observed with particular care in my own, is the rapid rise of the leukocytes after a fall to normal, and with a great decrease in the size of the previously enlarged organs. Actual observation must, of course, be the final test of such a matter, but it is easy to understand how a chronic leukæmia may have a sudden increase of circulating leukocytes, including cells not found normally in peripheral blood, or how a so-called pseudoleukæmia may become leukæmic within a short time. These observations do not throw any light on the process by which the new cells get into the peripheral vessels, but they prove that a long time is by no means necessary for a great excess of leukocytes to appear in the peripheral capillaries.

The Effects of Various Processes Other than Infection on Leukæmia.

Finding such striking effects on the leukocytes from the influence of infectious disease, one naturally asks whether other diseases or intoxications may not have similar consequences.

Oette[44] studied the effect of fevers on the course of leukæmia, at the instigation of Mosler, as long ago as 1879, but he was limited by the greater obscurity then surrounding both fever and leukæmia, and did not materially advance the subject.

Freudenstein[31] re-examined it in 1895. He gathered many interesting facts regarding the fever of leukæmia from the early literature, besides the histories of ten of the earliest cases of infection studied here. He concluded that fever is a frequent (63 per cent.) but not constant symptom of leukæmia, and ascribed this to substances derived from broken-down leukocytes, but did not study the possible results of such processes on the leukæmia itself, doubtless because of the difficulties surrounding such an investigation.

Marischler[52] reported a case of lymphatic leukæmia complicated by a Grawitz tumor of the right kidney. There was repeated hæmaturia, considered at first as a result of the leukæmia, but later more properly ascribed to the renal tumor. The leukocytes fell from 96,000 October 16th, 84,000 November 25th, to 48,000 on February 27th, and then rose to 72,000 on the last day. The polynuclears rose from 15.60 per cent. (or 21.70 per cent. at the beginning of the hæmaturia) to 57.60 per cent. The mononuclears fell from 82.30 per cent. (or 76.20 per cent.) to 40 per cent. The difference was still more marked in the blood of the last day. The changes were, therefore, qualitative rather than quantitative. Marischler explained the changes as due less to the hemorrhage than to the carcinoma toxin, a view I do not think free from error. Marischler gives theoretic reasons, based on experiments, for his view, but the passage of a necrotic bit of tissue, 1.5 cm. by 0.25 cm., shows that the explanation by changes following loss of blood is very near. The author gives the literature of new-growths complicating leukæmia, the only genuine cases he could find being those of Whipham and Lannois and Regaud. In these no effect of the cancer upon the leukæmia was noted.

The literature of leukæmia contains references to cases in which reduction of leukocytes had taken place under the most diverse drugs, such as iron, arsenic and its salts, phosphorus, quinine, oxygen, etc.; but it is suggestive that the drugs that some have found most valuable have failed entirely in the hands of others, without perceptible reasons in the cases themselves. Most of the reports give such scanty details of the blood in the stage of recovery that they cannot be utilized at present. The literature is largely available in the study of Vehsemeyer.[53]

The first to report a careful study of the process were Toulmin and Thayer,[54] who noticed a fall of from 714,000 to 7500 leukocytes in twenty-three days in a patient taking arsenic. Two weeks later there were 9500 leukocytes. The leukocyte formula changed from:

Lymphocytes	0.96	to	6.9
Polynuclear	70.0	to	83.2
Transition	3.0	to	2.5
Eosinophiles	2.3	to	3.0
Myelocytes	23.5	to	4.0

showing a relative increase of lymphocytes and polynuclears. The myelocytes, though much reduced, were still notably high, 4 per cent.

Bramwell[55] mentions a case in which the leukocytes fell from 210,000 to 1600 in thirty-eight days under treatment with arsenic, CO_2, and oxygen, and remained below normal for a month. There was fever and an eruption from unknown cause, so that the case, perhaps, should be included among the infections. The formula was altered as follows:

	Sept. 28.	Oct. 9.	Oct. 15.	Oct. 21.	Nov. 4.
Polynuclear	69.0	70	91	75	62
Myelocytes	26.5	25	3	5	7
Lymphocytes	3.5	5	5	20	31
Eosinophiles	1.0	1+	1+	0	0

Cabot[56] and d'Allocco[57] have reported cases in which the leukocytes fell to normal or below, but, at least in the former case, myelocytes were always present, and in a degree that would in itself excite the suspicion of leukæmia, or, in the absence of acute symptoms, suggest some serious disease of the bone-marrow requiring careful observation.

McCrae,[58] however, published a case in which there was not only no leukocytosis, but no sign of medullary disease. A man, aged twenty-eight years, had medullary leukæmia with a blood count in the spring of 1898 of 2,680,000 red cells, 584,000 leukocytes. He was put on arsenic, and in August there were only 184,000 leukocytes, and the spleen was barely palpable. In September there were 9250 leukocytes. Arsenic was continued, but in November the leukocytes numbered 178,000. In December there were 98,000; in April, after taking 10-drop doses of Fowler's solution, 5000 per c.mm. The myelocytes numbered 20 per cent. to 23 per cent. in the high stage, but were absent in the low one. The polynuclear leukocytes were 86 per cent. with 9250 leukocytes, normal with 5000. Mast-cells were present only once, in the relapse. Nucleated reds were absent after the first fall.

Taylor[59] has reported 3 cases in which the excessive leukocytes disappeared under the influence of arsenic. The improvement lasted for months, and then relapsed in all cases. A second stage of improvement followed in all; in 2 a third. The changes were qualitative at first, and varied both in quality and quantity at different times. In 1 case all qualitative changes disappeared, and a slight lymphocytosis was the only evidence of blood disease. In the other cases myelocytes persisted to the extent of 1 per cent. to 3 per cent., part eosinophilic. Taylor's discussion of this subject can be read with advantage by all who carry out experiments in the treatment of leukæmia. As in the case of infections, the low leukocyte count does not ensure recovery from the disease. This is shown by many reported cases, including the remarkable one of Saundby,[12] in which the white cells dropped from 540,000 to 8000 in eleven days, but death occurred in coma some weeks later.

It must be remembered that many of the patients whose cases are cited in the early part of this study were taking arsenic, sometimes in large doses, yet I think no one will ascribe the changes wholly or even in part to the drug in all cases. I may add that personally I have never seen a fall below 50,000 leukocytes in leukæmia from arsenic, but in only a small proportion of my cases was it possible to push the drug as it should be.

Under other drugs besides arsenic changes have been observed in the blood count in leukæmia. Von Jaksch[60] treated a patient with thyroiodin and cupric arsenate and noted a fall of from 295,000 to 560,000 to 28,000 in thirteen days, the blood at the latter count giving the picture of leukocytosis with few nucleated reds. The liver became smaller, even before the leukocytes fell. For five weeks the leukocytes were not above 100,000, but in six days reached the former high figure and remained there. Thyroiodin was also given during the rise. The formula two days before the lowest count was: polynuclears, 74.04 per cent.; mononuclear neutrophiles, 10.71 per cent.; polynuclear eosinophiles, 0.70 per cent.; mononuclear eosinophiles, 0.35 per cent.; small lymphocytes, 14.55 per cent.; large lymphocytes and transitional, 3.70 per cent. Basophiles were few at all times, and absent in the earlier examinations.

Pollitzer[61] reported a case of acute leukæmia, in which the leukocytes fell from 91,875 to 8500 in the course of seven days, while the patient was taking quinine in gram doses; fever continued; the spleen grew smaller. The patient died twenty-three days later. Postmortem the picture was that of acute anæmia gravis with lymphoid hypertrophy of the spleen, intestinal tract, bone-marrow and lymph glands. The author attributes the effect to the quinine, but the fever and the fatal termination suggest that it was due to something else, either an intoxication from the products of cellular break-down or an infection.

In another case of Pollitzer quinine was used in 1.5-gram doses with a rise and subsequent fall, leaving the leukocytes higher than before. The author cites a case of Kuehnau and Weiss,[62] in which a patient with Hodgkin's disease was given pilocarpine and developed acute leukæmia. Sabrazès says that in a case of leukæmia with malaria quinine injections had a happy effect, not only on the malaria, but also on the course of the leukæmia.

Richter and Spiro[63] treated a patient with splenolymphatic leukæmia and apical tuberculosis with cinnamic acid. Intravenous injections of very small doses of this caused the leukocytes to increase within three hours from 170,000 to 560,000. There was also a slight increase of red cells. Polynuclear cells increased from 45 per cent. to 86 per cent.; mononuclears fell from 55 per cent. to 14 per cent.; eosinophiles, scanty before, increased, and nucleated red cells appeared, but the increase of leukocytes soon disappeared. In twenty-four hours the original number was reached; four days after the first injection the number was 46,000, and it then gradually rose to the former point. The process was repeated in two more injections. The spleen and lymph glands grew smaller; the general symptoms improved. The author points out that the experiment shows how much more intensely the diseased hæmatopoietic organs react to irritants than do normal ones, and he compared the results of his experiments with those in some of the cases studied in this paper.

A number of observations have been published on the action of organic extracts and bacterial products upon the leukæmic subject.

H. Heuck[64] at an early period gave tuberculin injections in a patient with leukæmia, who had slight signs in one apex, but no bacilli in the sputum, and no reaction to 5 milligrams of tuberculin. Doses of from 10 to 120 mg., in nineteen injections, caused reactions like those in phthisis. From the twelfth injection (60 mg.; the leukocytes were not counted before) there was a fall in the number of leukocytes each time, quickly returning, though not quite to the previous number; so that at the end of the observation the proportion was 1 to 48 instead of 1 to 57. There was general improvement, with diminution in the size of the glands.

Pal[29] also used tuberculin in a leukæmic patient, and noted a slight decrease of leukocytes after six hours, followed next day by a rise. In three days the number was 154,000 in place of 134,000, and the glands were larger, but the leukocytes fell to 103,000. A week later with 135,000 leukocytes the polynuclear cells were increased, the temperature and subjective symptoms worse.

Beitzke[65] [15] used tuberculin in 6 leukæmic patients in Quincke's clinic. The results were very uncertain, the injections not being continued long enough to permit conclusions to be drawn and other treatment being carried out at the same time. Two patients that gave most distinct evidences of improvement were taking arsenic.

Pollitzer[61a] gave tuberculin in a case of medullary leukæmia in doses of 2 to 200 mg., without reduction of leukocytes, but with increase in the size of the spleen and more marked cachexia. In a case of lymphatic leukæmia tuberculin was given for two weeks in doses of 2 to 64 mg., with a gradual but slight rise of leukocytes, without change in the formula.

Nuclein (Horbaczewski's) was also used by Pal in the case mentioned above, with a fall of leukocytes, but with enlargement of the glands. Pal purposely avoided marked reactions in his experiments, in order to prevent severe effects on nutrition. Pollitzer also used nuclein in both cases cited above. In the first 2-gram doses given for five days had no effect. In the other case there was a slow and immaterial fall, followed by a rise.

Jacob[66] used splenic extract in a patient with leukæmia, giving it subcutaneously at intervals of two to four days. The injections were followed by sweating, anxiety, and dyspnœa, symptoms that Jacob had observed in animals treated with organic extracts, and which he attributed to a leukocyte congestion of the lung capillaries. There was a slight rise in the number of leukocytes, after the early injections, followed by a fall to about half the number present before the experiment was begun. As there was an increased excretion of nitrogen in the urine, Jacob also concluded the injections increased the breaking down of leukocytes.

Here may be mentioned Franke's[67] attempt to use an extract of leukæmic glands. A packet of glands from a case of lymphatic leukæmia was rubbed up with physiological salt solution and kept sterile. Injected into rabbits in doses of 5 c.c. to 10 c.c. there were evidences of breaking down of leukocytes. On account of the patient's condition the treatment could not be carried out as intended.

From these few experiments we learn little more than the need of others, and also something of the practical difficulties of such experiments. The blood must be examined at short intervals after the treatment is given, differential counts must be made, and an almost limitless range of work may be found in studies of the cytolytic conditions at various stages. The careful observation of the body and the subjective symptoms and studies of the metabolism, as shown by the urine, are also desired.

There are still other cases on record that illustrate possibilities in leukæmia.

Strattmann[68] reported a remarkable case, in which a patient with enlarged spleen and leukocytes and red corpuscles in equal proportions underwent an exploratory operation on the supposition that the enlargement of the spleen was due to malignant disease. After considerable manipulation of the spleen for diagnostic purposes, and following massage of the organ in order to overcome possible bad effects of the manipulation, the removal was abandoned, and the patient made a good recovery, so that not only was the spleen smaller, but the blood count was 5,300,000 red corpuscles; leukocytes, 1500.

This may be contrasted with Parker's case, referred to in the early part of this paper. In this a patient with old tuberculosis and enlarged spleen, but negative blood count ("the large lymphocytes seemed more numerous"), was explored, with a view to removal of the spleen. Soon after this the blood was markedly leukæmic.

Here we may allude to Senn's[69] interesting case of leukæmia "cured by Roentgen rays." The symptoms of intoxication, such as high temperature, make one wonder whether there was an intoxication from the absorption of broken-down products of spleen and blood, or, perhaps, an accidental infection, and reports of other cases treated by the same method will be awaited with interest. It is to be hoped also that in such reports the blood will be fully described.

A full and satisfactory explanation of the changes observed in leukæmia under the influence of other diseases does not seem possible at present. We are still too much in the dark regarding the cause of leukæmia, the nature of thechanges in the tissues and the mechanism of the blood changes, and we are only beginning to learn something of the effects of infection and intoxication on the blood-forming organs and the circulating blood. The work done by Muir,[70 71] Dominici,[72] Werigo and Jegunow,[73] Rubinstein,[74] Lengemann,[75] Roger and Josué,[76] Weil,[77] Flexner,[78] Bunting,[79] and others opens up a most promising field, but at present does not go far in explaining the difficulties in this particular subject.

An early and natural explanation was that diseases associated with leukopenia, or without leukocytosis in ordinary cases caused in leukæmia a decrease of leukocytes. This might apply to miliary tuberculosis, or typhoid fever, such as Eisenlohr's case was supposed to be. But further reports not only opposed this view, but even led to the opposite one, viz., that diseases ordinarily causing leukocytosis have an antagonistic effect in leukæmia.

Ortner[80] offered a plausible explanation, viz., consumption of the body, due to infection, but Beitzke pointed out some important objections. It does not account for the altered leukocyte formula often observed; the change sometimes comes on early, before the exhaustion of the body is evident; at other times leukæmia shows advanced wasting and cachexia without notable change in the leukocytes. H. F. Mueller's theory is attractive chiefly because of its obscurity. He suggested an "alterative" action, but in the present state of our knowledge this does not explain anything. The leukocytolytic theory of Fraenkel is also attractive. It seems borne out by the author's observations on degenerated leukocytes in his own cases, and the increased excretion of uric acid. It seems analogous to the rapid disappearance of certain tumors, some of which (sarcomata) closely resemble leukæmic growths, under the actions of poisons like arsenic, or those of certain infections, as erysipelas. Recently the chemotactic theory has become more prominent, and has received the support of Ehrlich, whose influence in the study of leukæmia is deservedly so great. Quincke's objection, that no evidences of transfer of leukocytes are present, might be explained by a rapid breaking down of the cells.

It seems to me the process in most cases is complex. Breakdown and consumption must occur in cases with severe cytolytic poisons, and in some must preponderate. In others chemotactic processes will be most important, and innumerable variations in the clinical course and the blood picture will probably depend partly on the kind, extent, and intensity of the intoxication, partly on the histological peculiarities of the new-growths, and the capacity of their cells to enter or be poured into the circulation. Thus, in acute lymphatic leukæmia, the changes will not be the same as in the chronic myeloid alteration of all the blood-forming organs.

Finally, the question as to therapeutic bearings must be met. It is easy to understand how many have looked upon the changes observed in cases cited above as evidences of healing. The most striking sign of leukæmia, the excess of leukocytes, disappears, and sometimes the spleen and lymph glands return to their normal size. Yet that the change is not wholly favorable appears from the fact that no case has really recovered. Most patients died while still under the influence of the process that was thought to have healed them, and, although some seem to have had their lives prolonged, none have lived longer than many leukæmics without such complications.

Weil has suggested that the action of the complicating infections is too "brutal," and this may be so, although the cases hitherto observed show considerable variation in severity. But, considering the hopelessness of the ordinary treatment of leukæmia, it seems that carefully planned experiments, either with bacterial products or organ extracts, might show a more safe and permanent result. I need not go into the details of such experiments, but may point out the necessity of thoroughness of the observations as an essential. Previous experience with the substances to be used, either on men or animals, is desirable, while a familiarity with the methods of blood examinations is indispensable.

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CARCINOMA OF ABDOMINAL CAVITY; PUNCTURE OF INTESTINE DURING PARACENTESIS ABDOMINIS; PRESENCE OF CARCINOMATOUS FRAGMENTS IN ASCITIC EXUDATE.

REMARKS ON CYTODIAGNOSIS.

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THE following case is of interest as showing the difficulty of diagnosis of abdominal disease, the danger of even the most carefully performed paracentesis, and the value of microscopic examinations of exudate, etc.

Mrs. B., aged sixty-eight years, complaining of abdominal distention, dyspnœa, indigestion. Family history unimportant; acute Bright's disease twelve years ago, with apparent complete recovery as far as symptoms showed. Six months previously the patient noticed